

In Situ Product Recovery of β -Ionone from a Fermentation Broth: Computational Solvent Selection and Process Design of Its Extraction and Purification

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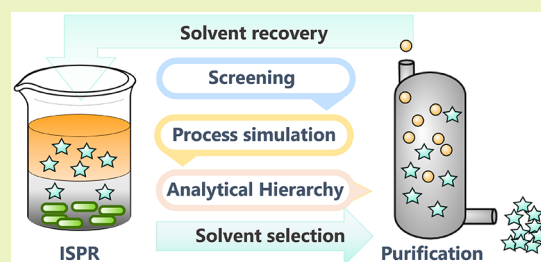
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ABSTRACT: Flavors and fragrances are important compounds used in the food, cosmetic, and pharmaceutical industries. They have an added value in the market when obtained through natural processes instead of synthetic routes. β -Ionone raises special interest if produced through a biotechnological process with genetically modified *Sacharomyces cerevisiae*, which is considered a natural production alternative. The main problem is that β -ionone is toxic to *S. cerevisiae* when its concentration increases in the fermentation broth. However, an *in situ* liquid–liquid extraction can alleviate the toxicity problem by removing the solute when it is produced. Thus, a screening of 6012 solvents for liquid–liquid extraction was performed by predicting the partition coefficient of β -ionone between an aqueous and an extracting organic phase using COSMO-RS. The best solvents for β -ionone extraction were selected after evaluating several parameters like solvent–water mutual solubility, solute extraction capacity, boiling temperature, thermophysical properties, and life cycle assessment of the solvent. The process was simulated and optimized in Aspen Plus V10 where *in situ* extraction was considered as a liquid–liquid extraction unit and the purification as two distillation towers in series. Then, a multicriteria decision-making analytical hierarchy process was performed based on the screening and simulation results with a subsequent sensitivity analysis. Finally, extracting solvents selected with the previous methodology were 2-methyl-2-butanol, 2-methyl-3-butene-2-ol, methyl isobutyl ketone, 1-pentanol, 1-octanol, myrcene, and *n*-decane, which were compared with the performance of dodecane, the benchmark extracting solvent used in the literature. Branched alcohols appear as a promising family of compounds for extracting β -ionone from aqueous phases.

KEYWORDS: β -Ionone, Screening, COSMO-RS, Liquid–liquid equilibrium, ASPEN Plus



INTRODUCTION

Flavors and fragrances, also called aromas, are compounds found in fruits, plants, and animals. They are highly demanded by food, pharmaceutical, and cosmetic industries because they confer specific organoleptic properties to the final products that are attractive to the final consumers.¹ Nowadays, an increase of 3.5% in demand for aromas is reported with annual sales of US\$ 40 billion in 2020.² Thus, it is essential to find efficient and sustainable production alternatives for obtaining a higher amount of aromas and satisfying the increasing demand.

Typical methods for the production of aromas are extraction from natural sources or chemical synthesis.^{3,4} Both alternatives present advantages and disadvantages. For instance, aromas obtained from natural products, like fruits, can be labeled as natural if the extraction uses green processes and harmless solvents. However, some specific aromas are present in trace amounts in the raw material requiring high amounts of the matrix, and in some cases, a large amount of solvent is needed for the extraction, making the process not feasible.⁵ On the other hand, the chemical synthesis of aromas is cheap and

efficient, but the product has a lower price compared with its natural analogue. Also, in a number of cases, the product is a racemic mixture that is difficult to separate.^{6,7} Moreover, there is an increasing negative perception of the consumers toward products obtained from synthetic sources due to the sensation that traces of unhealthy compounds could be present in the final product. However, some synthetic aromas are labeled as natural-like, meaning that the product is free of traces of potentially toxic compounds; nevertheless, the natural version of the aroma typically has a higher price compared with the natural-like version.⁸ Thus, alternatives for the natural production of aromas are intensely studied in order to obtain a valuable product with an efficient and sustainable process.

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An interesting process for producing natural aromas are the biotechnological production by biotransformations using enzymes for converting natural precursors and *de novo* synthesis based on fermentation.^{6,9} In general, biotransformations are a viable process with larger yields than *de novo* synthesis. However, the production of aromas via *de novo* synthesis has been improved by genetically modifying the producing microorganism through metabolic engineering, which leads to overproducing the target product in the fermentation broth.¹⁰ Biotechnological production can provide aromas with high enantiomeric purity and a good selectivity but undesirable side products, low yields, or the toxicity of the aroma on the producing microorganism could be detrimental for designing a profitable biosynthetic process.^{6,7,11} Thus, an *in situ* product removal (ISPR) technique is required for improving the performance of the process by removing the aroma as soon as it is produced.^{12,13}

ISPR is a set of techniques that can be used coupled to the biotechnological production in order to remove a target product when it is produced.¹² The objective of ISPR is to reduce the toxicity on the producing microorganism, reduce the number of downstream processes, decrease the product losses, or remove other undesirable side products. This can be a decisive factor in the bioprocess viability, since it has been reported that the downstream cost can be more than 50% of the process total cost.¹⁴ Numerous research studies have investigated the energy usage associated with ISPR. For instance, a comparison was made between the energy consumption during the production of butanol by fermentation, with and without ISPR revealed that the perstraction step in ISPR consumed slightly less energy than the conventional fermentation method without ISPR. However, the purity of the final product was not optimal when compared to solvent extraction.¹⁵ Another study showed that hybrid extraction–distillation technology consumed 30 times less energy than conventional gas-stripping applied in the production of esters using fermentation.¹⁶ ISPRs technologies have been used in conjunction with membranes with techniques such as membrane distillation, ionic exchanger, pervaporation, and micro-/ultra-/nanofiltration^{17,18} on two-phase systems such as solvent extraction,^{19,20} stripping,¹⁴ adsorption,^{21,22} and other alternatives like reactive extraction, electrodialysis, crystallization, and precipitation.^{17,19} Liquid–liquid extraction or solvent extraction of the biosynthesized compound from the aqueous phase using a nonpolar compound is a promising technique due to the large amount of solvents than can be selected and its high potential to be scaled toward an industrial application. However, solvent selection is challenging and requires us to obtain certain characteristics to find a good candidate for the process. For instance, the solvent should have a high selectivity and high distribution ratio for the solute, low cost, biocompatible with the producing microorganism, nonvolatile, nonmiscible with the aqueous phase, etc.^{23,24} Also, the ideal solvent should be easily separated from the solute in order to decrease the further steps of purification.²³ Liquid–liquid removal has been used for extracting fermentation products from the aqueous phase, for example, products like 2-phenylethanol,²⁵ β -ionone,¹⁰ *n*-butanol,²⁶ and *p*-coumaric acid,²⁷ among many others.

β -Ionone is an aroma present in small amounts in several flowers and fruits as violets, apricots, raspberry, blackberry, etc. It is used as flavor and fragrance in food and cosmetic products due to its woody and violet-like scent.⁹ In nature, β -ionone is

the precursor of β -carotene and vitamin A, but it is also naturally bioconverted by the enzymatic cleavage of β -carotene.¹ Most of the production of β -ionone is synthetic and is used not only as a final product but also as an intermediary for synthesizing other molecules. Natural β -ionone is typically produced by extraction from natural sources and its biotechnological production has been reported.⁴ Bacteria and yeasts are the most widely used microorganisms at an industrial level, but since they cannot naturally produce ionones, it is been necessary to apply *de novo* synthesis and genetic modifications using heterologous genes.^{4,9,21,28} Several engineered yeast strains have been studied for producing β -ionone by fermentation, like *Escherichia coli*,²⁹ *Sacharomyces cerevisiae*,^{10,28} and *Yarrowia lipolytica*,⁴ with a maximum yield of 500 mg/L.²⁹ The main issue is that β -ionone is toxic, for example, for *S. cerevisiae* at low concentrations.¹⁰ Therefore, an ISPR technique is required for improving its natural production by biotechnological means. The removal of β -ionone from the aqueous fermentation broth has been performed *in situ* using pervaporation^{30,31} and liquid–liquid extraction with dodecane as solvent.¹⁰ Nevertheless, dodecane is a highly nonpolar aliphatic compound, and we need a polar solvent, either protic or aprotic, which will be an effective β -ionone extractant. This is explained by the presence of the ketone and alkene groups on β -ionone, which give this molecule polarity and thus the ability to form hydrogen bonds.^{27,32,33} For example, using dodecane and dodecanol over the extraction of *p*-amino benzoic acid, the hydroxyl group in the dodecanol achieved extraction efficiency 37 times higher than dodecane.³² On the other hand, to our knowledge, a comprehensive selection of potential extracting solvents for *in situ* liquid–liquid extraction of β -ionone and a process design for its purification have not been reported in the literature.

Since there is scarce experimental thermodynamic information about β -ionone in literature, a predictive tool for calculating the partition coefficient of the aroma in a solvent–water system is required to select a potential liquid–liquid extracting solvent. This is an important task to reduce the number of experiments for designing the *in situ* aroma extraction. CONductor-like Screening Model for Real Solvents (COSMO-RS) is a predictive quantum chemistry-based thermodynamic tool that uses only a σ -profile of the compounds as the input.^{34,35} Different implementations of the COSMO-based models have been proposed, such as COSMO-SAC,³⁶ Modified COSMO-SAC,³⁷ COSMO-RS based electrolyte model,³⁸ and different versions of COSMO-RS updated in the COSMOTermX software.³⁹ COSMO-RS has been tested as a successful screening tool for several applications, i.e., for selecting organic solvents for extracting furfural and 5-hydroxymethylfurfural from water,⁴⁰ ionic liquids for H₂S capture,⁴¹ deep eutectic solvents (DES) for BTX (benzene, toluene, and xylene) extraction from aliphatics,⁴² and extracting solvents for solubilizing artemisin,⁴³ among others. In fermentation processes, COSMO-RS model has been previously used for screening and solvent selection for the recovery of several classes of bioproducts such as 2-phenylethanol,^{44,45} 2,3-butanediol,⁴⁶ butanol,^{47–51} 1,5-pentanediamine,⁵² succinic acid,^{53,54} L-lactic acid,⁵⁴ L-malic acid,⁵⁴ and vanillin,⁵⁵ using a wide range of solvents from conventional organic to tailor-made solvents such as ionic liquids or DES. Also, COSMO-based/Aspen Plus methodology is a tool that has allowed the computational design of different processes like the removal of H₂S from flue gases using ionic

liquids,⁴¹ the capture of siloxanes from biogas using ionic liquids,⁵⁶ the optimal selection of solvents for aromatic/aliphatic separations,^{57,58} ionic liquids for extracting the aroma 2-phenylethanol from water,³⁹ etc.

The objective of this work is to select potential solvents for *in situ* liquid–liquid extraction of β -ionone from a fermentation broth using COSMO-RS as the screening tool. Dodecane is used as the base case since there is information in the literature about its use in the ISPR of β -ionone,¹⁰ and it has a low mutual solubility with water. Thus, the aim is to find solvent alternatives that produce a higher partition coefficients of β -ionone in the solvent–water model mixture compared with dodecane. Also, health, environmental, and safety (HSE) rules using the CHEM21 assessment are considered for the solvent selection.⁵⁹ Once the best alternatives are chosen, the design of the extraction and purification of β -ionone is performed with Aspen Plus, with a COSMO-based model (extraction) and UNIFAC-Dortmund (purification) as the thermodynamic tools. The extraction process was simulated using a one plate liquid–liquid extraction unit and the purification process by distillation.^{60,61} The complete process was optimized for each solvent. All the properties of the solvents along with their performance in the extraction/purification processes are assessed in order to select the best alternatives based on a multicriteria decision-making analysis. To this end, two scenarios are considered: recovering at least 99% of the mass of β -ionone or obtaining a purity of β -ionone of 99 wt % in the exit stream. Then output variables such as the distillate-to-feed ratio, reflux ratio, temperature towers (boiler and condenser), and heat consumed by every tower (boiler and condenser), among others, are compared to each solvent.

MATERIALS AND METHODS

Solvent Screening. The screening of solvents for extracting β -ionone from water was performed using COSMO-RS implemented in COSMOTermX (version 18.0.2) and its parametrization BP_TZVP_C30_1701. First, the geometry of β -ionone was obtained in Turbomole 7.0 at BP86/TZVP computational level, searching for the structure of minimum energy, with the solvent effect through the COSMO continuum solvation method. Once the optimization was finished, the polarized charge distribution of β -ionone is obtained by a COSMO single point calculation, saving it into a *.cosmo file. The solvent database used for the screening is 02_BP-TZVP-COSMO from COSMOTermX.⁵⁶

The screening was performed by assuming a ternary system composed by β -ionone + water + extracting solvent. Then, the partition coefficient at infinite dilution ($\log K$) is obtained by calculating the activity coefficient at infinite dilution for β -ionone in the water phase ($\gamma_{\beta}^{\infty,w}$) and the solvent phase ($\gamma_{\beta}^{\infty,s}$) at 298.15 K and 101.15 kPa as shown in eq 1:

$$\log K = \log \frac{x_{\beta}^s}{x_{\beta}^w} = \log \frac{\gamma_{\beta}^w}{\gamma_{\beta}^s} \approx \log \frac{\gamma_{\beta}^{\infty,w}}{\gamma_{\beta}^{\infty,s}} \quad (1)$$

where x_{β}^n and γ_{β}^n are the compositions or activity coefficients of β -ionone, respectively, in the phase n which is water (w) or solvent (s). Also, the boiling point of the respective solvent and the liquid–liquid equilibrium of the binary system solvent + water was calculated at 298.15 K and 101.15 kPa using COSMO-RS.

Criteria for Screening Solvents. Partition coefficients were calculated with COSMO-RS for β -ionone using all the solvents included in the screening, comparing the results with the value observed for dodecane as a benchmark solvent. As mentioned before, dodecane is used as the base case because it has been used previously in the *in situ* extraction of β -ionone from a fermentation broth,

showing biocompatibility with the yeast.¹⁰ First, all the solvents that produced a lower partition coefficient than dodecane were discarded. Moreover, the solvents that showed a boiling temperature below 333.15 K were removed because they could require special process conditions due to their volatility. Also, the solvents have to show a partial miscibility with water; otherwise, they are discarded. However, if the solvents dissolve at mass fractions over 0.03 in the water-rich phase, then they were also discarded because a higher concentration could increase the toxicity problems for the producing microorganism and there would be a higher solvent loss during the extraction. Finally, the solvents were analyzed in their life cycle with the HSE assessment using the CHEM21 methodology, where those evaluated as highly hazardous are discarded.⁵⁹ After this process, eight solvents that were representatives of different chemical families were selected as potential extracting solvents for the next step. The criteria is further shown in Figure S1.

Process Design of the Extraction/Purification Steps. The liquid–liquid extraction and purification of β -ionone was designed by simulation using Aspen Plus V10 with the thermodynamic property package Modified COSMO-SAC and UNIFAC-Dortmund, respectively. The σ -profiles were added to the simulator as SGPRF (σ -profiles segments in Aspen Plus) for the selected solvents. The same COSMO volume (CSACVL) was used as in the screening section (COSMOTermX with parametrization BP_TZVP_C30_1701). Aspen Plus V10 does not incorporate the latest version of COSMO-RS with which the screening was carried out. Thus, the simulation was carried out using Modified COSMO-SAC, because it accurately reproduces the predictions of COSMO-RS (COSMOTermX) for the liquid–liquid equilibrium at 303.15 K and 101.3 kPa between water and all the selected solvents for β -ionone extraction, as shown in Figure S2.

The simulation of the liquid–liquid extraction was performed in a FLASH3 unit at 303.15 K and 101.15 kPa. The extractor was fed with an aqueous flow of 180 kg·h⁻¹ (10 kmol·h⁻¹) with a concentration of β -ionone of $w_{\beta\text{-ionone}} = 5.42 \times 10^{-3}$ ($x_{\beta\text{-ionone}} = 2.82 \times 10^{-5}$, equivalent to the concentration achieved in fermentation by Lopez et al.)¹⁰ and the respective solvent in a second stream. In the extractor for all solvents, the solvent-to-feed (S/F) ratio was optimized until obtaining a 99.9% of recovery of β -ionone, i.e., at least a 99.9% of the mass of β -ionone is recovered in the solvent phase compared with the fed flow.

The exit mixture obtained from the liquid–liquid extractor, i.e., the solvent, the extracted β -ionone, and some concentration of water removed, was fed into the first distillation unit of the solvent recycling and aroma purification stage. The selection of the distillation is based on two main reasons. First, it is possible to achieve high purity and recovery rates during solvent recycling. Second, it is necessary to eliminate any trace of solvent in the aroma stream affecting its odor. Likewise, distillation is among the most commonly used process in the pharmaceutical industry for solvent recycling. For example, Pfizer uses distillation for solvent recovery from small-volume waste streams from specialty chemicals (i.e., active pharmaceutical ingredients) manufacturing.⁶² Moreover, several authors have pointed out the suitability of integrating liquid–liquid extraction and distillation for recovery and purification of added-value chemicals from fermentation broth.⁶³

Then, the β -ionone-rich stream at the exit of the first tower was fed to the second distillation unit. Both towers were simulated as a RADFRAC unit in equilibrium mode with UNIFAC-Dortmund as the thermodynamic package. The first tower was simulated with 8 stages with the feed in the plate number 6. The second tower had 15 stages, and the feed was located in the plate number 8. There were two different scenarios considered for studying the purification steps. First, an exit flow of the second tower with a recovery of at least the 99% of the mass of β -ionone fed to the first tower, and second, a mass concentration of at least 99% of β -ionone in the exit of the second tower. In order to evaluate both cases, the distillate-to-feed (D/F) and reflux ratio were optimized in both towers. The range used for the D/F ratio was from 0.01 to 0.99, and for the reflux ratio was from 0.1 to 5. A diagram of the process for extracting and purifying β -ionone is depicted in Figure 1

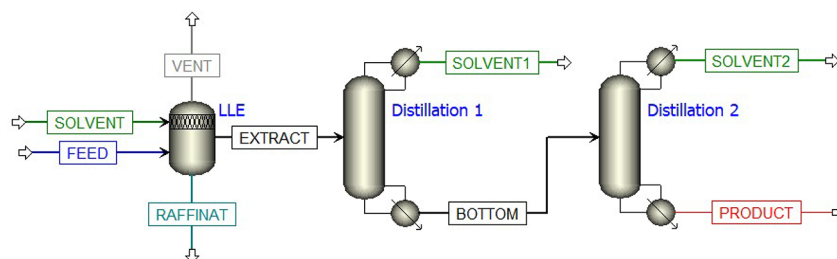


Figure 1. Process simulation of the extraction of β -ionone from water using Aspen Plus V10. (1) Liquid–liquid extractor. (2) and (3) Distillation towers for purification of β -ionone.

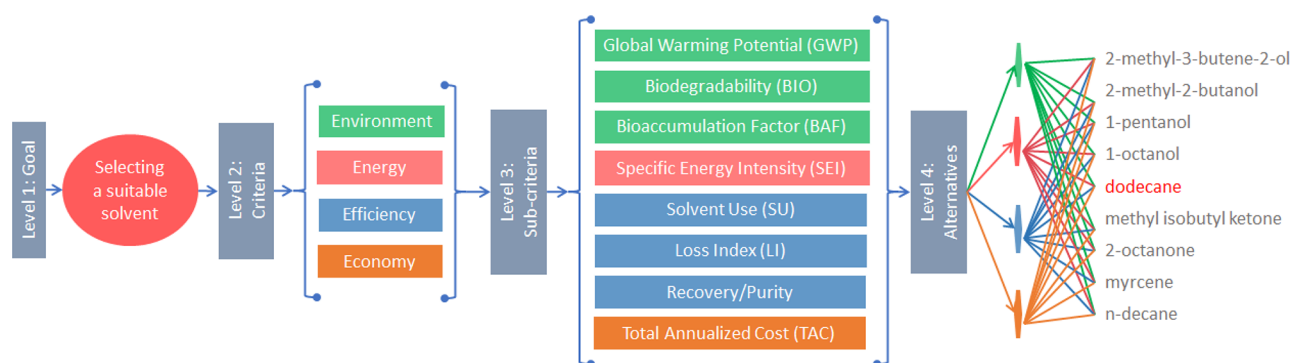


Figure 2. AHP model structure for selecting a suitable solvent for extracting β -ionone.

Table 1. Parameters for Selected Solvents in This Work for the Extraction of β -Ionone from Water^a

name	CAS	M_W (g·mol ⁻¹)	T_{eb}^{cosMO} (K)	w_s^s	w_s^w	log K	HSE ^c
2-methyl-3-butene-2-ol	115–18–4	86.13	404 (372) ^b	0.89	2.5×10^{-2}	3.42	R
2-methyl-2-butanol	75–85–4	88.15	389 (375) ^b	0.88	1.5×10^{-2}	3.00	P
1-pentanol	71–41–0	88.15	411 (411) ^b	0.86	1.3×10^{-2}	2.92	R
1-octanol	111–87–5	130.23	469 (467) ^b	0.94	5.4×10^{-4}	2.82	R
MIBK	108–10–1	100.16	392 (389) ^b	0.92	1.8×10^{-2}	2.81	R
2-octanone	111–13–7	128.21	447 (446) ^b	0.96	1.8×10^{-3}	2.69	R
myrcene	123–35–3	136.23	431 (443) ^b	1.00	1.1×10^{-5}	2.62	P
<i>n</i> -decane	124–18–5	142.28	429 (447) ^b	1.00	7.9×10^{-7}	2.14	R
dodecane	112–40–3	170.33	472 (489) ^b	1.00	0.0	2.07	P
β -ionone	79–77–6	192.30	608 (539) ^b	0.94	1.6×10^{-3}		

^aCAS number, molar mass (M_W), HSE recommendation, and some properties calculated with COSMO-RS like boiling temperature (T_{eb}^{cosMO}), mass fraction of the solvent in the organic (w_s^s) or aqueous phase (w_s^w) for the binary system solvent + water, and the log of the partition coefficient of β -ionone (log K) in the solvent/water system. ^bValues in parentheses retrieved from Aspen Plus V.10. ^cR = recommended, P = problematic. Criteria are available in Figure S3

Analytical Hierarchy Process for Solvent Selection. Selecting a suitable solvent for extracting β -ionone from the fermentation broth is a multidimensional problem. Multicriteria decision-analysis (MCDA) tools can be used to tackle this complexity. However, selecting the most appropriate MCDA methodology is complicated and sometimes hard to support without a consensus regarding which approach best fits a specific application.⁶⁴ Among the MCDA methodologies, it is well-documented that Analytical Hierarchy Process (AHP) has been successfully applied to solvent selection problems in the pharmaceutical industry, recovery of added-value products, e.g., palm oil and carotenoids, solvents molecular design, and selecting sustainable routes in early design stages.^{64–68} Moreover, AHP provides a framework for consistently quantifying decision priorities.⁶⁹ Besides, qualitative and quantitative criteria can be integrated into the same analysis, mainly when expert judgments are a relevant part of the decision-making process. Thus, AHP was chosen as the MCDA methodology in the present study.

The AHP was developed in four steps: (i) break down the decision into a hierarchical model, (ii) priorities derivation for the main criteria, (iii) derivation of local and overall (model synthesis) priorities, and (iv) sensitivity analysis. Figure 2 shows the model hierarchy structure (four levels) for the decision process. The first level is our goal, i.e., selecting a suitable solvent. The main criteria, i.e., Environment, Energy, Efficiency, and Economy, from which the selection is based comprise level 2 and considered the four sustainability indicators defined in the taxonomy for chemical processes.⁷⁰ The performances of the solvents were compared quantitatively based on subcriteria included in level 3. Finally, level 4 of the model included all the alternatives (results from the screening) being considered to satisfy the goal. Indicators in levels 2 and 3 were pairwise compared based on judgments of experts considering Saaty's scale of 9 points.⁶⁹ Likewise, normalized values of attributes in level 3 were used to compare the alternatives and synthesize the model. To account for inconsistencies in the

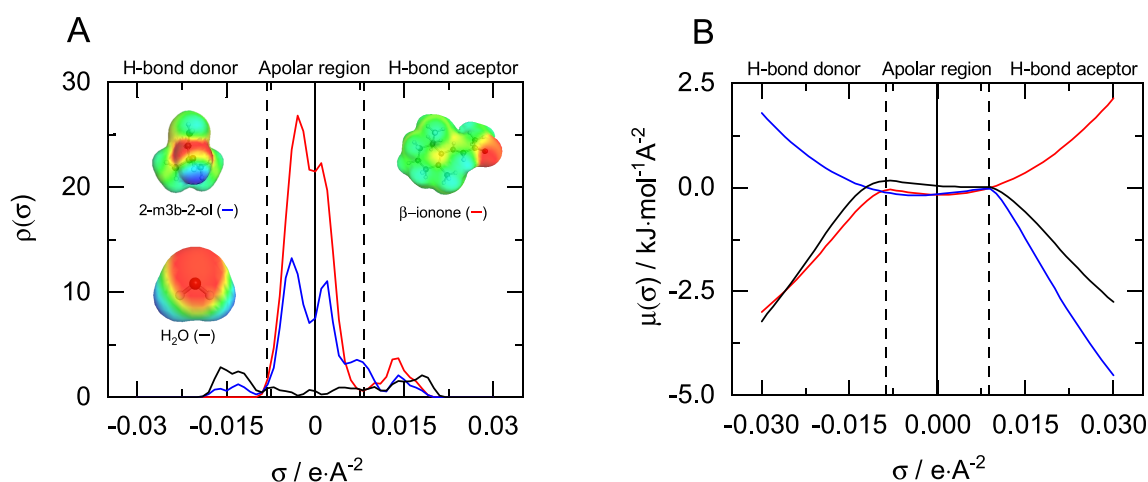


Figure 3. (A) σ -Surface and σ -profile. (B) σ -Potential of β -ionone (red), 2-methyl-3-butene-2-ol (blue), and water (black).

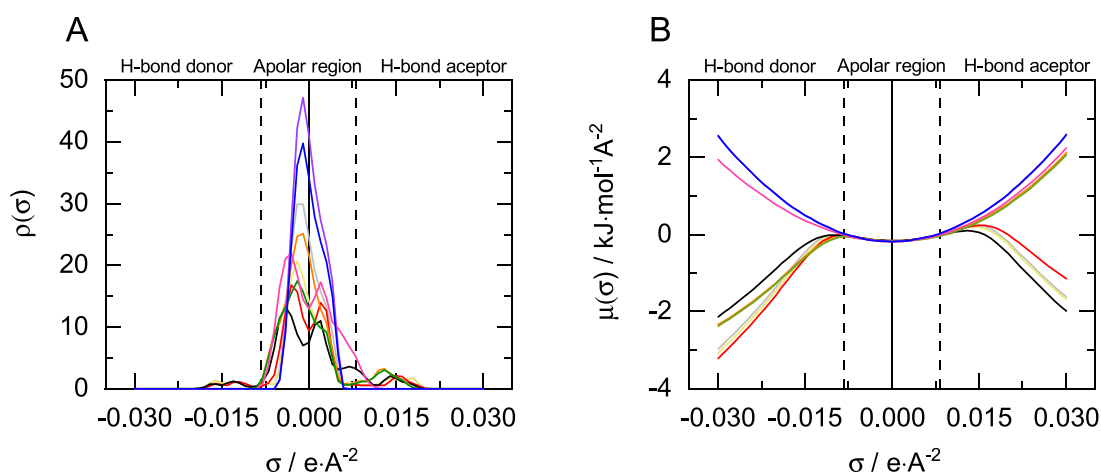


Figure 4. (A) σ -Profile and (B) σ -potential of 2 methyl-3-butene-2-ol (black), 2-methyl-2-butanol (red), 1-pentanol (yellow), 1-octanol (gray), 4-methyl-2-pentanone (green), 2-octanone (orange), myrcene (magenta), *n*-decane (blue), and dodecane (purple).

comparisons, the consistency ratio (CR) was calculated. If the CR \leq 0.1, then the inconsistency is considered acceptable.⁶⁹ Details of the AHP calculation procedure are out of this article scope and can be consulted elsewhere.^{65,66,69} The assumptions made for quantifying attributes in level 3 are mentioned in the results section. To test the robustness of the decision model, a sensitivity analysis on the weighting factors in the pairwise comparison in levels 2 and 3 was carried out.

RESULTS AND DISCUSSION

Solvent Screening for β -Ionone Extraction. All solvents with a lower partition coefficient than dodecane or that were partially miscible with water were eliminated. Furthermore, solvents with boiling temperatures higher than 333.15 K were considered because they do have no volatility problems. Also, if the solvents dissolve at mass fractions over 0.03 in the water-rich phase they were also discarded to avoid toxicity and lost solvent problems. The selected solvents as potential extracting agents for β -ionone were branched alcohols such as 2-methyl-3-buten-2-ol and 2-methyl-2-butanol, linear alcohols such as 1-pentanol and 1-octanol, ketones as 4-methyl-2-pentanone (MIBK) and 2-octanone, and aliphatic hydrocarbons such as myrcene and *n*-decane. All of them were compared with dodecane in terms of the experimental boiling point and properties calculated with COSMO-RS as boiling temperature, mutual solubility with water, and the partition coefficient of β -

ionone in the water–solvent system calculated with eq 1. In addition, the analysis of HSE aspects of the solvents were evaluated according to the CHEM21 methodology.⁵⁹ All the information about the selected solvents is shown in Table 1. Branched alcohols and MIBK, which have shown biocompatibility in other yeasts,⁷¹ have a similar boiling point compared to water, while the rest of the solvents have a boiling point between 400 and 500 K. These values are far from the boiling point of β -ionone (339 K) allowing the separation via distillation in the downstream process. The estimated solubility of all the solvent in the aqueous phase is below 0.03 in mass fraction. Still, without considering the aliphatics, most of them show a considerable amount of water in the solvent-rich phase. Then, it is necessary to remove moisture and the solvent to purify the β -ionone. Alcohols produce the highest partition coefficient values of β -ionone, promoting them as a good option instead of dodecane. However, given their higher water absorption during the liquid–liquid equilibrium and their boiling points close to water, there are additional assessments to consider for evaluating if these kind of solvents can be recovered and reused in the process. Other considerations such as the purity of the β -ionone, the amount of water/solvent in the final product, and solvent/product losses must be considered. Most of the selected solvents are recommended according to the HSE assessment, except for aliphatic

hydrocarbons that are cataloged as problematic, because *n*-decane and dodecane have high boiling points, and myrcene requires special handling and waste treatment due to toxicity and irritation problems.

According to the log *K* predictions with COSMO-RS, 2-methyl-3-butene-2-ol (2-m3b2-ol in Figure 3A) is an interesting compound for extracting β -ionone from water. This solvent provides insights on how the sigma profile and sigma surface of the good solvents should be. Figure 3A shows the σ -surface and σ -profile, and Figure 3B shows the σ -potential for 2-methyl-3-butene-2-ol, water, and β -ionone. It can be seen that β -ionone has a large nonpolar site (mostly green area in the σ -surface) composed of the surroundings of the cyclic carbons and the H-bond acceptor group (red area in the σ -surface) composed of the free electrons around the oxygen in the ketone group. Then, the partial miscibility of water with β -ionone is explained by the large H-bond acceptor group of water that could cause some repulsion between the ketone group and the large nonpolar group of the β -ionone. On the other hand, a molecule like 2-methyl-3-butene-2-ol would be a good solvent for β -ionone due to its H-bond donor group (blue area in the σ -surface) that would interact with the H-bond acceptor group of β -ionone. Also, the σ -potential shows that β -ionone has a higher affinity with a H-bond donor molecule; meanwhile, 2-methyl-3-butene-2-ol has the ability to interact as a H-bond acceptor or H-bond donor.

The σ -surface of the selected solvents is shown in Figure S4, and their σ -profile and σ -potential are shown in Figure 4. It is observed that those solvents with a larger H-bond donor capacity show the highest partition coefficient of β -ionone. There are two classes of solvents: those with high affinity with a H-bond donor and a peak in the nonpolar region in the σ -profile. The others have low affinity for both groups because the σ -profile area is only in the nonpolar region. The first class of solvents, except for myrcene and ketones, show affinity for H-bond donor and H-bond acceptor molecules in the σ -potential. A balance in the solvent is needed, for instance, a H-bond donor group to form hydrogen bonds with the β -ionone but without a high association with water. Therefore, a big H-bond donor group implies a better solvent for extraction but a bigger miscibility in water. As seen in Table 1, solvents with higher log *K* value show the highest miscibility with water. This effect can also be seen in the σ -potentials of the Figure 4B. On the other hand, myrcene and the ketones have an H-bond acceptor group similar to β -ionone but do not form hydrogen bonds with the solute and show van der Waals and Misfit interactions. Also, they have affinity for H-bond donor solvents, just like β -ionone. The solvents in the second group are dodecane and *n*-decane which show the lowest log *K* but the highest immiscibility with water according to Table 1. β -Ionones have only van der Waals interactions in the nonpolar groups with those solvents which explains the lower values of distribution coefficients.

Binary Interactions. To understand the binary interactions between the selected solvents and β -ionone, the excess enthalpy, and Gibbs energy were calculated using COSMO-RS. Figure 5 shows the equimolar excess enthalpy (Table S1) and Gibbs energy (Table S2) for the solvents with β -ionone. In all cases, the Gibbs energy has the same tendency as the excess enthalpy, and enthalpic contributions are predominant in most cases, as observed in Table S2. The solvent with the biggest log *K* values, 2-methyl-3-buten-2-ol, shows an exothermic behavior due to strong hydrogen bonding. The van der Waals is the

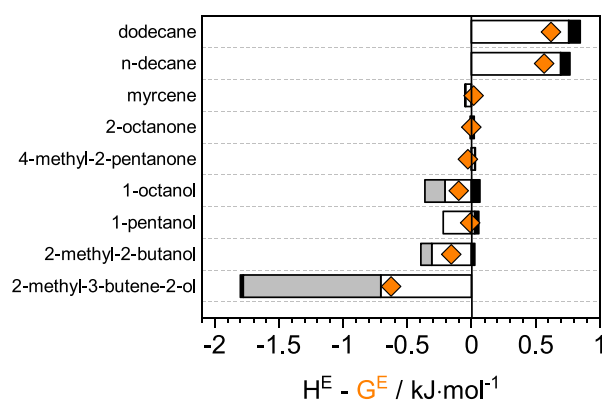


Figure 5. Excess enthalpies (H^E) contributions (MF, HB and VdW) and excess Gibbs energy (G^E) for an equimolar mixture of solvents with β -ionone. Contributions: MF (black bar), HB (gray bar), VdW (white bar), and G^E (orange diamond).

largest contribution to the excess enthalpy for the selected solvents, except for 2-methyl-3-butene-2-ol. The Misfit interactions are negligible in all cases. The alcohols show an exothermic behavior, while the myrcene is slightly exothermic, the ketones are slightly endothermic, and aliphatic chains like decane and dodecane show an endothermic behavior. A higher exothermic behavior of the solute–solvent mixture is associated with a better ability for such solvent to extract the specific solute.⁷² Thus, branched and linear alcohols appear as the best option for extracting β -ionone under these terms. On the other hand, Figure S5 shows the excess enthalpy, excess entropy, and excess Gibbs energy for different concentrations of β -ionone and water, showing a low affinity between unlike molecules.

Liquid–Liquid Extraction. In order to evaluate the model predictions by Modified COSMO-SAC, ternary systems of water + β -ionone + solvents were calculated in Aspen Plus V10 and compared with COSMO-RS from COSMOthermX (Figure S6 and Tables S3–S12) showing a good agreement between both models. Then, for each solvent, the liquid–liquid extraction was simulated and the minimum S/F ratio required to recover 99.9% of β -ionone was determined (Figure 6). In this regard, *n*-decane and dodecane require the highest S/F ratio until ten times more than the selected solvents, because of the low affinity with β -ionone. This causes the process flow for aliphatic solvents in the simulation evaluation to be large, which finally subsequently affects the selection criteria, despite having low solvent loss. 1-octanol and myrcene show better

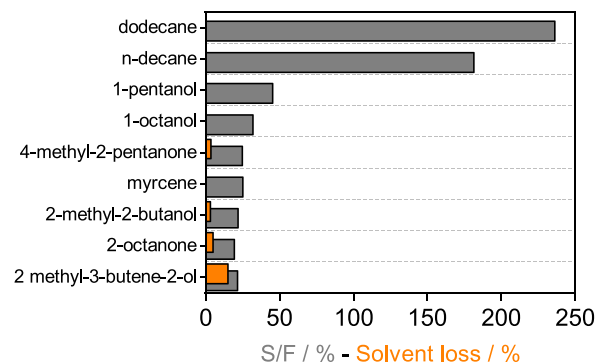


Figure 6. Solvent to feed (gray) and solvent loss (orange) percentage for recovery of 99.9% of β -ionone.

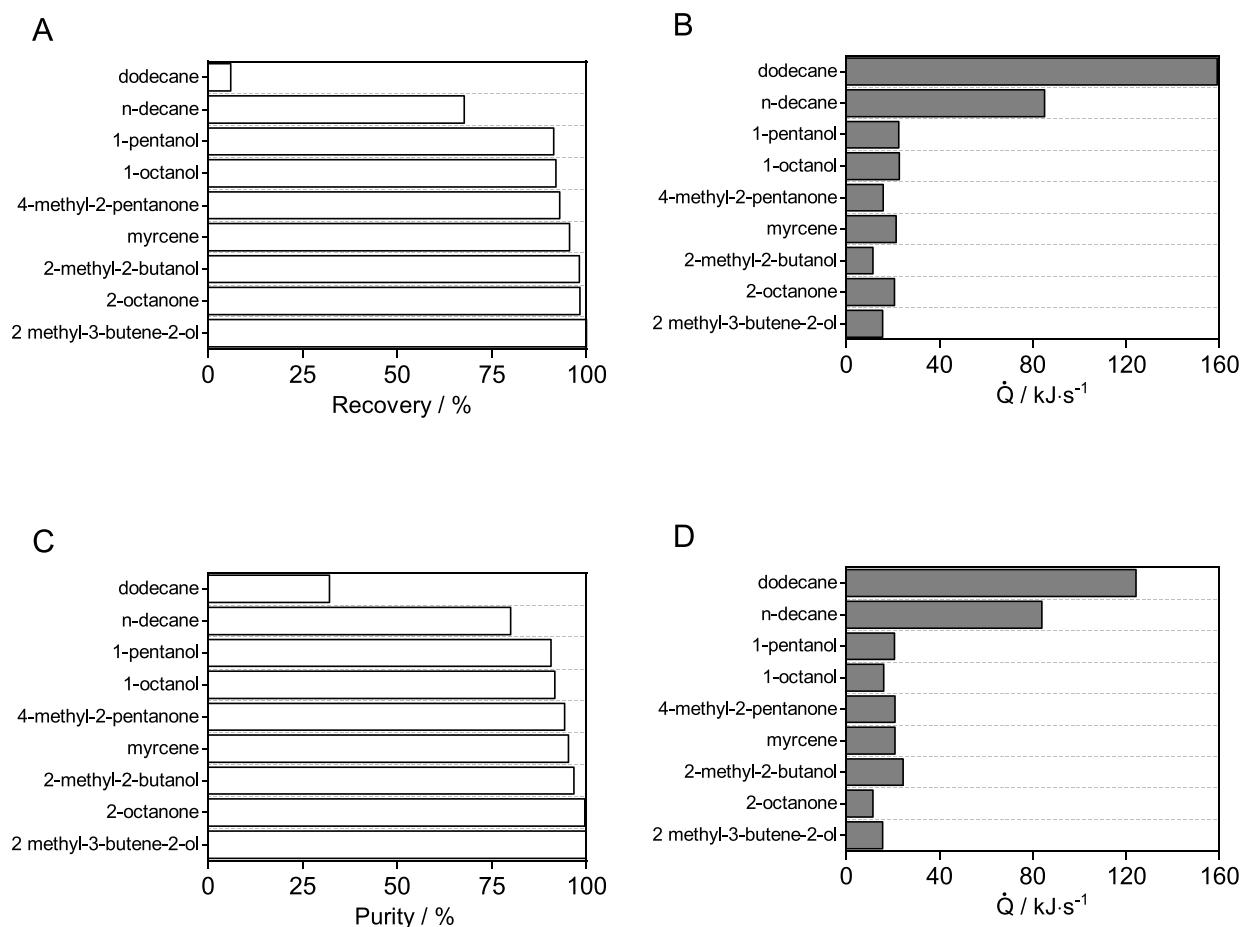


Figure 7. Simulation results for recovery of purity (white) and reboiler heat (gray) for two scenarios. The target for scenarios (A,B) is a 99% purity of β -ionone, and the target for scenarios (C,D) is a 99% recovery of β -ionone.

behavior, obtaining a low S/F ratio and low solvent loss. Overall, based on these indicators (S/F and solvent loss), it seems that 1-octanol and myrcene are the most suitable candidates for the extraction of β -ionone. On the other hand, 2-methyl-3-buten-2-ol, which appears as a good candidate in terms of excess enthalpy, shows the lowest S/F ratio but is the alternative with the highest solvent loss into the water phase. However, as it is discussed later in this work, the solvent selection is a multidimensional task, and more criteria should be considered beyond the parameters considered in this section.

Aroma Purification. After the extraction process the two distillation towers for aroma purification were simulated using the UNIFAC-Dortmund model (parameters are shown in Table S12) independently for the scenarios of 99% of recovery and 99% of purity of the solute. The first tower was used to remove as much water as possible without losing aroma from the column top. The second tower was designed to purify the aroma.^{73,74} In all cases, both towers were optimized in terms of the total annualized cost by using the in-built optimization toolbox in Aspen Plus V10. Details of the optimization function are shown in the Supporting Information. The function of the first tower was to reduce the amount of solvent and remove water from the product stream. The input of the second tower was a mixture of solvent and β -ionone. The simulation results of each tower are shown in the Tables S13–S15.

Figure 7A,B shows the results of obtaining a 99% purity of β -ionone using all the selected solvents. Since all the solvents have the same recovery, the comparison was based on the purity of the product stream. The heat of the reboiler of both towers was compared to study the main operating cost of running the distillation. Dodecane shows the worst performance in terms of β -ionone purity and the reboiler duty. This behavior could be explained by the close boiling temperature between both compounds. Meanwhile, 2-methyl-3-butene-2-ol shows the best performance with a 99% of purity and recovery and one of the lowest requirements of reboiler duty. Also, the second best performance was observed for 2-methyl-2-butanol showing that both branched alcohols are good alternatives for separating and purifying β -ionone. All the selected solvents show a final β -ionone purity above 85% except for 1-pentanol, *n*-decane, and dodecane. Also, most of the solvents show a reboiler duty below 25 kJ/s; however, *n*-decane and dodecane present values above 80 kJ/s. In consequence, *n*-decane and dodecane are not recommended for the extraction process due to the issues during the purification of β -ionone.

Figure 7C,D shows the results for a recovery of a 99% in mass of β -ionone. 2-Methyl-3-butene-2-ol is the only solvent able to achieve a recovery of 99.9%. Nevertheless, the rest of the selected solvents have a recovery of at least a 80% of β -ionone. In terms of the reboiler duty, the results are similar compared with the previous case.

Solvent Prioritization. Once the list of suitable solvents has been defined (including HSE restrictions) and assessed

from the thermodynamic point of view (i.e., partition coefficient), the final selection of the top candidates is based on a multicriteria decision-making analysis (i.e., the AHP methodology), where the assumptions made for quantifying attributes in level 3 are shown in the Supporting Information (Tables S16–S19). Table 2 shows the criteria priorities at

Table 2. Priorities from the Pairwise Comparison

levels	criteria	priorities		consistency ratio
		normal	ideal	
2: main criteria	efficiency	0.438	1.000	0.077
	environmental	0.352	0.804	
	economic	0.139	0.317	
	energy	0.071	0.162	
3: environmental	GWP	0.594	1.000	0.052
	BAF	0.249	0.419	
	BIO	0.157	0.264	
	recovery/purity	0.666	1.000	
3: efficiency	solvent use	0.166	0.500	0.000
	loss index	0.166	0.500	

levels 2 (main criteria) and 3 (subcriteria) along with their consistency ratio (CR) for both studied cases (i.e., recovery and purity at 99% each). The Economic and Energy subcriteria (Figure 2) were directly used for synthesizing the model without any associated subcriteria in Table 2. All pairwise comparisons were consistent (i.e., CR < 0.1), ensuring the quality of the results. At level 2, the Efficiency indicator was the top priority (0.438), scoring ~20% higher than the Environmental one. This result reflects the experts primary concern is the efficiency of the process, i.e., the liquid–liquid extraction, when selecting the most appealing solvents. Solvent selection is usually prioritized based on physical attributes, e.g., partition coefficient, selectivity, and solvent capacity, with a high impact on the process efficiency, ensuring the solvent functionality in the first place.^{66,75} In contrast, Rosinha–Grundtvig et al.⁷⁶ argue that solvent selection should start by assessing the HSE attributes followed by the physical ones, e.g., recovery and recyclability, and finally fulfill the specific bioprocess application. In order to cover these two approaches, a sensitivity analysis was carried out, and the results are discussed later in this section. At level 3, the global warming potential subcriteria priority (+50%) revealed the necessity of industrial bioprocesses with a low carbon footprint. Likewise,

depending on the target design (recovery/purity), these were considered the top priority among the efficiency indicators.

Figure 8 shows the results of the synthesized model obtained for each studied case. Overall, 2-methyl-2-butanol resulted in the most suitable solvent regardless of the design target, i.e., recovery/purity, based on the values of each impact factor (level 3) (Tables S16–S19). A recent study has shown that long-chain alcohols can reduce toxicity during ISPR, improving the product yield.⁷⁷ In this regard, an experimental study has to be undertaken to test solvent biocompatibility. Moreover, dodecane ranked as the least suitable candidate among the considered solvents. The ideal priorities from each assessed design target are also shown in Figure 8. Ideal priority measures how appealing a solvent is compared to the top-ranked one (2-methyl-2-butanol). When recovery of $\geq 99\%$ of the aroma is the design target, myrcene was 95% as appealing as 2-methyl-2-butanol, slightly higher the 2-methyl-3-butene-2-ol (93%). On the other hand, when the product purity $\geq 99\%$ is the design target, 2-methyl-3-butene-2-ol became 92% as appealing as 2-methyl-2-butanol, followed by the MIBK (77%). These results suggested that the loss index and energy intensity highly influenced solvent prioritization for recovery 99% of the aroma and product purity of 99%, respectively. Changes in the rest of the impact factors did not seem significant in the final ranking.

Variations in the relative preferences of each criterion assigned by the experts in levels 2 and 3 (Figure 2) can lead to different outputs from the AHP. Thus, a sensitivity analysis was performed to test the robustness of the final decision. To this end, seven scenarios were analyzed as shown in Table 3. For

Table 3. Case Criteria Used in Sensibility Analysis

case	criteria
case 1	All main criteria were equally weighted, 25%.
case 2	All environmental subcriteria were equally weighted, 33.3%.
case 3	All efficiency subcriteria were equally weighted, 33.3%.
case 4	Environmental criteria weighted, 100%.
case 5	Efficiency criteria weighted, 100%.
case 6	Energy criteria weighted, 100%.
case 7	Economic criteria weighted, 100%.

example: (1) All main criteria, i.e., environmental, efficiency, energy, economic, were equally weighted (25%) concerning the goal. (2) All environmental subcriteria, i.e., bioaccumulation factor (BAF), biodegradability (BIO), and global warming

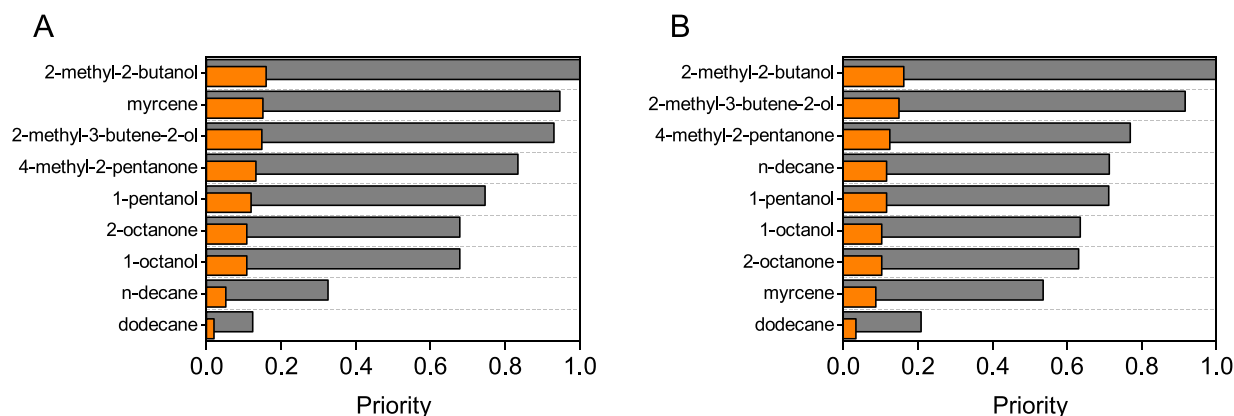


Figure 8. Priority results from the synthesized AHP model (A) recovery 99% and (B) purity 99%. Ideals values (gray) and normals values (orange).

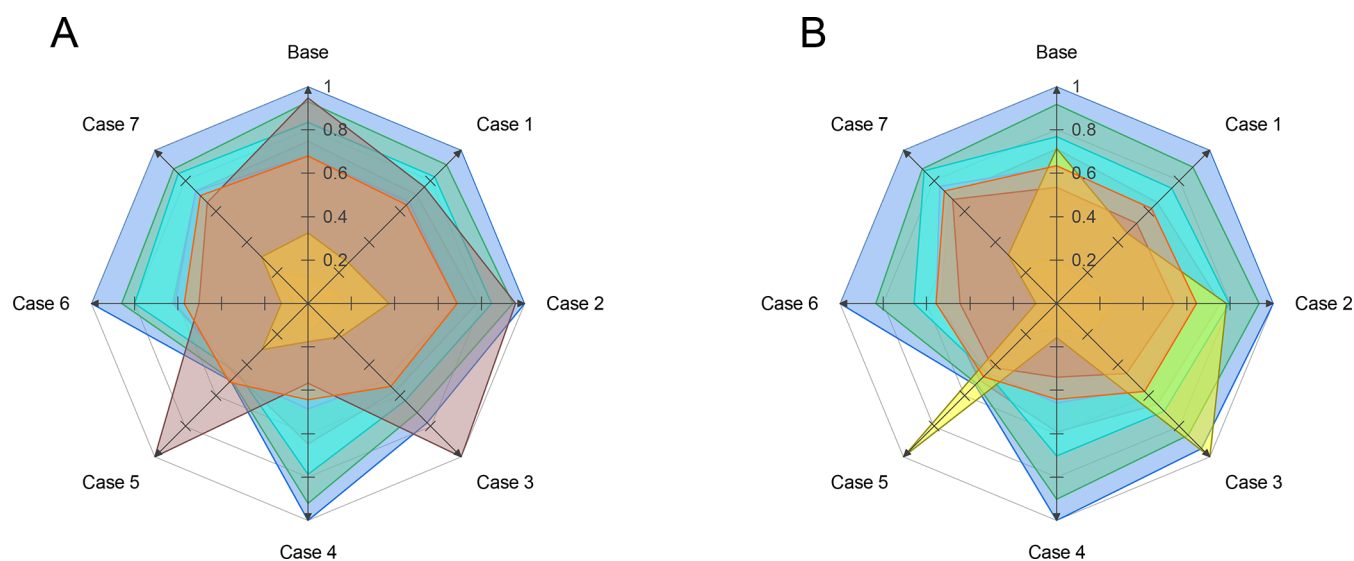


Figure 9. Case analysis for selected solvents. (A) purity 99% and (B) recovery 99%. Solvents: (lilac) 2-octanone, (cyan) 4-methyl-2-pentanone, (orange) 1-octanol, (pink) 1-pentanol, (blue) 2-methyl-2-butanol, (green) 2-methyl-3-buten-2-ol, (yellow) decane, (brown) myrcene, and (gold) dodecane.

potential (GWP), were equally weighted (33.3%). (3) All efficiency subcriteria (i.e., solvent use, loss index, recovery/purity) were equally weighted (33.3%). (4–7) Only one of the main criteria weights 100%, while the others were kept at 0%.

Figure 9 shows the results from the sensitivity analysis for both design targets. Overall, no variation in the top priority decision, i.e., 2-methyl-2-butanol, was obtained regardless of the design target in 75% of the cases (including the base case). Meanwhile, 2-methyl-3-butene-2-ol ranked as the second-best solvent ($\approx 69\%$ of the cases), while MIBK scored the third-best one ($\approx 63\%$ of the cases) for both design targets. Moreover, dodecane remained the least appealing solvent in 100% of the studied cases. Likewise, only cases 3 (efficiency subcriteria weighted 33.3% each) and 5 (efficiency criteria weighted 100%) 2-methyl-2-butanol was shifted from the top position under both design targets, closely related to the impact of the loss index indicator in the decision. The critical impact of solvent loss on process performance has been highlighted previously based on rigorous process evaluation.⁷⁵ Summing up, the results from the sensitivity analysis showed good stability, leading to 2-methyl-2-butanol, 2-methyl-3-butene-2-ol, and MIBK as the most likely solvents for dodecane replacement for extracting the aroma.

CONCLUSIONS

A thermodynamic strategy for solvent selection was carried out in a liquid–liquid extraction process of β -ionone from a fermentation broth. Extracting solvents selected were 1-octanol, 1-pentanol, 2-methyl-3-butene-2-ol, 2-methyl-2-butanol, MIBK, 2-octanone, and *n*-decane. Dodecane was tested as a benchmark solvent but obtained the worst performance of the chosen solvents due to low $\log K$, high boiling point, highest S/F, and big requirement energy for the purification step. Solvents selected as potential β -ionone extractants are recommended for their use according to the CHEM21 methodology. However, 2-methyl-2-butanol, myrcene, and dodecane could be problematic.

Simulation results show 2-methyl-3-butene-2-ol was a good alternative for ISPR, as 99% purity and 99.9% recuperation were achieved after purification. Also, the solvent consumed

the lowest energy in the purification step. Nevertheless, this solvent has a limitation: it is slightly miscible with water. On the other hand, 1-octanol was the best solvent in the liquid–liquid extraction despite his lower $\log K$. The selection of the best solvents depends on multiple criteria. For example, if the main focus is minimizing the solvent used for the extraction of β -ionone, then the best three solvents are 2-octanone, 2-methyl-2-butanol, and 2-methyl-3-butene-2-ol. Otherwise, if the focus is preventing the solvent loss, then the recommended solvents are 1-pentanol, 1-octanol, and myrcene.

Finally, a sensitivity analysis on multicriteria decision-making parameters was performed to obtain insights into solvent selection. These results recommended 2-methyl-2-butanol, 2-methyl-3-butene-2-ol, and MIBK as the most likely solvents for dodecane replacement in β -ionone extraction from fermentation broth. The next step in the solvent validations is the study of the feasibility using a biocompatibility experiment to see which solvent is applicable in ISPR; otherwise, they could be excellent alternatives for membrane-assisted liquid–liquid extraction or other separation techniques.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.3c01739>.

Thermodynamic parameters obtained by COSMO-RS; LLE calculations of β -ionone + water + solvent; UNIFAC parameters; simulations process results; normalized AHP values for levels; framework scheme; COSMO-RS vs COSMO-SAC; σ surfaces of selected solvents; excess properties of selected solvents with COSMO-RS; LLE of selected solvents with β -ionone + water; HSE criteria evaluation; additional details on AHP subcriteria (PDF)

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The manuscript was written through contributions of all authors. All authors have approved the final version of the manuscript.

Notes

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